Docket No.: 27656/38365A
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ernst Hafen et al.

Application No.: 10/509,558 Confirmation No.: 1027

Filed: March 25, 2005 Art Unit: 1649

For: GROWTH REGULATING PROTEINS Examiner: G. S. Emch

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Barbara Froesch, declare the following:

1. I graduated in 1992 from the Swiss Federal Technology Institute (ETH) in Zurich, where I studied pharmaceutical sciences. After the Ph.D. work in the Department of Oncology at the University Hospital of Zurich, I dedicated three years to the study of tumor biology in Dr. John Reed' s laboratory at The Burnham Institute in La Jolla, CA, USA. I joined The Genetics Company, a spin-off of the University of Zurich and the ISREC of Epalinges, as a research scientist in January 1999 and I am currently head of the Biology Department and program manager cancer therapeutics.

2. I have reviewed the Official Action by the U.S. Patent Office dated March 17, 2006 and submit this declaration to address the issue of whether it was recognized at the time of applicants' invention that analysis of bodily fluids was a reliable methodology for diagnosing tumors. A review of the scientific literature demonstrates that the analysis of bodily fluids such as saliva, serum, urine, peritoneal fluid and bone marrow could be used for the diagnosis of non-haematopoetic tumors as set out in the publications below:

Publication	Set-up	Result
Hibi et al., "Molecular Detection of Genetic Alternations in the Serum of Colofectal Cancer Patients," *Cancer Research* 58: 1405-1407 (1998)	Microsatellite analysis of genetic alterations in **serum DNA** obtained from 44 **colorectal cancer** patients.	"Taken together, either a K-*ras* or p*53* mutation was detected in the serum in 40% of the 25 patients (95% confidence interval, 21-61%), whose primary tumors contained a mutation and in 23% of the 44 patients (95% confidence interval 12-38%) with colorectal cancer. The frequent detection of mutations in the *p53* tumor suppressor in the serum of patients with early stage tumor suggests a possible use of this approach for clinical prognosis and cancer monitoring of colorectal cancer patients."
El-Naggar et al., "Genetic heterogeneity in saliva from patients with oral squamous carcinomas:implications in molecular diagnosis and screening," *J Mol Diagn.* 3(4):164-70 (2001).	Microsatellite analysis of **head and neck squamous carcinoma** (HNSC) on **saliva** and matched tumors in 37 patients.	-"epithelial cells in saliva[...]provide suitable material for genetic analysis" -in 49% of patients genetic alterations (LOH) could be detected in saliva
Spafford et al.," Detection of head and neck squamous cell carcinoma among exfoliated oral mucosal cells by microsatellite analysis," *Clin Cancer Res.* 7(3):607-12 (2001).	Microsatellite analysis of **saliva** in **head and neck squamous cell carcinoma** (HNSCC) patients.	Microsatellite instability was detected in 96% and LOH in 61% of cases with corresponding genetic alterations in the primary tumors.
Lauschke et al., "Detection of APC and k-ras mutations in the serum of patients with colorectal cancer," *Cancer Detect Prev.*	Detection of K-ras and APC mutations in **serum DNA** of **colon** cancer patients.	Mutations in the K-ras oncogene only found in the serum of 6/22 patients but mutations in the APC tumor suppressor found in serum of 20/25 patients

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25(1):55-61 (2001).		
Schott et al., "Isolated tumor cells are frequently detectable in the peritoneal cavity of gastric and colorectal cancer patients and serve as a new prognostic marker," *Ann Surg.* 227(3):372-9 (1998).	**Bone marrow** or **peritoneal cavity fluid** of **gastric** or **colorectal** patients were investigated immunocytochemically.	Little prognostic significance of positive bone marrow results but high correlation of results from peritoneal cavity fluid and survival rate.
Kersting et al., "Differential frequencies of p16(INK4a) promoter hypermethylation, p53 mutation, and K-ras mutation in exfoliative material mark the development of lung cancer in symptomatic chronic smokers," *J Clin Oncol.* 18(18):3221-9 (2000).	**Sputum** analysis in **lung cancer** patients for the oncogene K-ras and the tumor suppressors p53 and p16.	Differences on DNA level could be detected in 14-51% of patients if the markers were analyzed individually but in 69% if the markers were combined.
Eisenberger et al., "Diagnosis of renal cancer by molecular urinalysis," *J Natl Cancer Inst.* 91(23):2028-32 (1999).	Microsatellite alterations in **urine** and **serum** of **renal cancer** patients.	Alterations could be found in 76% of urine samples and 60% of serum samples.
Vogel et al., "Disseminated tumor cells in pancreatic cancer patients detected by immunocytology: a new prognostic factor," *Clin Cancer Res.* 5(3):593-9 (1999).	Immunocytochemical analysis of **peritoneal cavity fluid** and **bone marrow** in **pancreatic cancer** patients.	In 39 and 38% of patients alterations could be found in peritoneal lavage or bone marrow, respectively. Combination of the two bodily fluids resulted in 52% of correctly diagnosed patients.
Weitz et al.,"Detection of disseminated colorectal cancer cells in lymph nodes, blood and bone marrow," *Clin Cancer Res.* 5(7):1830-6 (1999).	Expression analysis of CK by RT-PCR on **lymph nodes** (lymphatic system), **blood** and **bone marrow** samples of **colon cancer** patients.	CK detection in lymph nodes is of prognostic relevance.

Chang et al., "Molecular diagnosis of primary liver cancer by microsatellite DNA analysis in the serum," *Br J Cancer.* 87(12):1449-53 (2002).	Analysis for LOH in **serum** of **liver cancer** patients.	LOH found in 76.2% of patients.
Hickey et al., "Molecular detection of tumour DNA in serum and peritoneal fluid from ovarian cancer patients," *Br J Cancer* 80(11):1803-8 (1999).	Analysis of genetic alterations in **serum** and **peritoneal fluid** of **ovarian cancer** patients.	In 17/20 serum samples and 12/19 peritoneal fluid samples, genetic alterations could be detected.
A. Vogel et al., "Disseminated tumour cells. Their detection and significance for prognosis of gastrointestinal and pancreatic carcinomas". *Virchows Arch.* 439(2):109-17 (2001).	Review of the various **methods to detect disseminated tumor cells** used at that time and the prognostic relevance of the results gained from these studies.	"Our evaluation of the studies on colorectal, gastric and pancreatic ductal carcinomas indicates that detection of disseminated tumour cells in different compartments may lead to more accurate tumour staging."

3. These publications show that analysis of bodily fluids for the diagnosis of non-haematopoetic tumors was well accepted in the art at the time of applicants' invention because disseminated tumor cells or DNA of non-haematopoetic tumor cells can be found in nearly all bodily fluids (e.g., serum, saliva, bone marrow, peritoneal cavity fluid, sputum, urine, lymph nodes, and blood, as noted in the above publications). While negative results exist, they depend upon the marker/antigen/genetic alteration that is investigated. A striking example of this is the low significance in diagnosing colorectal cancer by the detection of mutations of the oncogene K-ras in comparison to mutation in the tumor suppressor genes APC or *p53* (see Lauschke et al. and Hibi et al.). However, both extra- and intracellular DNA have successfully been detected and analyzed in relation to tumor diagnoses of various cancers (see, e.g., Hibi et al., p. 1405, 1st column, which notes that "tumor DNA is released into circulation and is enriched in plasma and serum.").

4. In conclusion, tumor diagnosis by the analysis of bodily fluids is well accepted and state of the art. Low performance of certain methods is due to poor marker quality and/or tool selectivity (e.g. antibodies) rather than to the method as such. The present invention helps to solve this problem because it introduces a new tumor marker which is appreciably downregulated in certain tumors. In addition, in contrast to many other tumor markers, such as PSA, the biological function of Elp as growth suppressor has been shown experimentally (in the disclosure of the specification). Consequently, Elp has already undergone validation as a diagnostic tumor marker. Therefore, the present application establishes the status of Elp as a tumor growth suppressor, and the state of the art at the time of filing establishes the knowledge with respect to the ability to detect tumors in tissues and body fluids by the detection of such markers.

5. I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001.

Dated: August 8, 2006

Barbara Froesch

EXHIBIT LIST

Exhibit 1 – Declaration of Barbara Froesch Ph.D.

Appendix A - Hibi et al., "Molecular Detection of Genetic Alternations in the Serum of Colofectal Cancer Patients," *Cancer Research* 58: 1405-1407 (1998)

Appendix B - El-Naggar et al., "Genetic heterogeneity in saliva from patients with oral squamous carcinomas:implications in molecular diagnosis and screening," *J Mol Diagn.* 3(4):164-70 (2001).

Appendix C - Spafford et al.," Detection of head and neck squamous cell carcinoma among exfoliated oral mucosal cells by microsatellite analysis," *Clin Cancer Res.* 7(3):607-12 (2001).

Appendix D - Lauschke et al., "Detection of APC and k-ras mutations in the serum of patients with colorectal cancer," *Cancer Detect Prev.* 25(1):55-61 (2001).

Appendix E - Schott et al., "Isolated tumor cells are frequently detectable in the peritoneal cavity of gastric and colorectal cancer patients and serve as a new prognostic marker," *Ann Surg.* 227(3):372-9 (1998).

Appendix F - Kersting et al., "Differential frequencies of p16(INK4a) promoter hypermethylation, p53 mutation, and K-ras mutation in exfoliative material mark the development of lung cancer in symptomatic chronic smokers," *J Clin Oncol.* 18(18):3221-9 (2000).

Appendix G - Eisenberger et al., Diagnosis of renal cancer by molecular urinalysis," *J Natl Cancer Inst.* 91(23):2028-32 (1999).

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Appendix I - Weitz et al.,"Detection of disseminated colorectal cancer cells in lymph nodes, blood and bone marrow," *Clin Cancer Res.* 5(7):1830-6 (1999).

Appendix J - Chang et al., "Molecular diagnosis of primary liver cancer by microsatellite DNA analysis in the serum;" *Br J Cancer.* 87(12):1449-53 (2002).

Appendix K - Hickey et al., "Molecular detection of tumour DNA in serum and peritoneal fluid from ovarian cancer patients," *Br J Cancer* 80(11):1803-8 (1999).

Appendix L – Kasimir-Bauer et al., "Survival of Tumor Cells in Stem Cell Preparations and Bone Marrow of Patients with High-Risk or Metastatic Breast Cancer after Receiving Dose-intensive or High-Dose Chemotherapy," *Clin Cancer Res.* 7:1582-9 (2001).

EXHIBIT 1

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